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# The Role of MAPK and SCF in the Destruction of Med13 in Cyclin C Mediated Cell Death

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The role of MAPK and SCF in the destruction of Med13 in cyclin C mediated cell death.

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In response to stress, the yeast <sup>1</sup> and mammalian <sup>2</sup> cyclin C translocate from the nucleus to the cytoplasm, where it associates with the GTPase Drp1/Dnm1 to drive mitochondrial fragmentation and apoptosis. Therefore, the decision to release cyclin C represents a key life or death decision. In unstressed cells, the cyclin C-Cdk8 kinase regulates transcription by associating with the Mediator of RNA polymerase II. We previously reported that the Mediator component Med13 anchors cyclin C in the nucleus<sup>3</sup>. Loss of Med13 function leads to constitutive cytoplasmic localization of cyclin C, resulting in fragmented mitochondria, hypersensitivity to stress and mitochondrial dysfunction due to

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loss of mtDNA. Recently we showed that this molecular switch operates in a two step process. First, efficient cyclin C nuclear release requires its ROS-induced phosphorylation by the MAP kinase Slr2<sup>4</sup> in a carboxyl terminal region of cyclin C, which includes a putative Med13 interaction site. The second step involves ROS-induced Med13 destruction by the SCF<sup>Grr1</sup> ubiquitin ligase. Med13 associates with Grr1 in two-hybrid assays, and SCF mediated degradation of Med13 requires active cyclin C-Cdk8<sup>5</sup>. However, phosphorylation of Med13 by cyclin C-Cdk8 does not trigger Med13 destruction. This suggests a model in which this kinase primes the Med13 degron for SCF<sup>Grr1</sup> and either Slr2, or an as yet unidentified kinase, triggers its destruction. Taken together, these results are consistent with a model in which cyclin C phosphorylation by Slr2 permits its disassociation from Med13, and that Med13 destruction allows full cyclin C release and prevents re-accumulation of the cyclin in the nucleus.

<sup>1</sup>Dev. Cell. (2014), 28:161; <sup>2</sup>Mol. Biol. Cell. (2015), 26:1030; <sup>3</sup>Mol. Biol. Cell (2104) 25:2807; <sup>4</sup>Mol. Biol. Cell. (2014) 25:1396; <sup>5</sup>MBOC. (2017) submitted

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